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The method according to claim 1 wherein treatment of the cell population with the two or more immunotoxins causes low toxicity to CD34+ cells in the population.

REMARKS

The specification has been amended to correct typographical errors. No new matter has been introduced by these amendments. Claim 1 has been amended and new claims 15- 25 have been added to more clearly define the invention. Upon entry of this amendment, Claims 1, 3, 6-8, 13, and 14 -25 are pending in the application. Amendments to the claims have been made to place the claims in condition for allowance, or in a better form for appeal. Therefore, entry of this amendment is respectfully requested. A list of the pending claims are provided to the examiner for her convenience.

The previously amended Table 4, as detailed in the applicant's response to the Office Action mailed 7 August 2000 (Paper No 15), contains a clerical error. The amended Table 4 was intended to retain the data in the far right column indicating 1.0 µg/ml which shows a 2.5 log cell kill, not 0.1 µg/ml as indicated in the applicant's first response. It would have been obvious to one of ordinary skill in the art that, in light of the written specification, in particular Figure 1, that 0.1 µg/ml as detailed in Figure 4 was an error. Therefore, the amended Table 4 does not introduce new matter into the disclosure of the invention and the applicant respectfully requests removal of the objection under 35 U.S.C. § 132.

Claim Rejections - 35 U.S.C. § 112

Claims 1, 3 and 6-8 remain rejected under 35 U.S.C. 112, first paragraph for reasons set forth in Paper No. 13, Section 6, pages 3-6. The Office Action (Paper No. 16) states, "The [Applicant's previous] arguments have been considered but have not been found persuasive (a') for the reasons previously set forth drawn to the unpredictability of anticancer drug discovery and differences between in vitro assays and complex conditions of in vivo therapy." Applicants respectfully traverse the rejection.

Applicants respectfully assert that the probability of successfully killing malignant cells *in vivo* using the treatment as established *in vitro* is very high due to the 1) high specificity of the

antibodies, 2) the effectiveness of the combined immunotoxin approach 3) the low toxicity of the combined immunotoxin approach for non-malignant cells and, 4) previous data indicating the specificity of clinical localization of the Moc 31 antibody to tumor tissue compared to healthy tissue. The Applicant has demonstrated that the immunotoxin has a highly specific toxic effect on cancer cell lines but not on normal hematopoietic cells, including early progenitor cells. The early progenitor cells are highly sensitive to toxic effects of anticancer compounds, such as toxins, and the selective effect as demonstrated in the Applicant's current immunotoxin approach strongly argues for the same successful and selective effect *in vivo*.

It is generally accepted in the art that even though the transition from *ex vivo* to *in vivo* is complex, as indicated in the office action, this is the only accepted method for testing medicaments. Thus it is a general opinion in the art that it is not possible to test the effect of cancer medication, without a basis in *ex vivo* experiments as has been and is being done in large governmental and company drug screening programs.

Applicant respectfully requests reconsideration of this argument and request withdrawal of this rejection.

Claims 3 was rejected for the reasons previously set forth in Paper No. 13, Section 7, pages 6-9. The Office Action (Paper No. 16) indicates that neither antibody BM7 or MOC 31 are commercially available, are irrevocably available to the public with out restriction, or will be available if viable sample cannot be dispensed by S. Kaul or MCA Development, respectively.

Applicants provide information regarding the commercial availability of the BM7 and MOC 31 antibodies.

The monoclonal antibody BM7 can be obtained from:

MEDAC GmbH

Postfach 303629

D-20312 HAMBURG GERMANY

tel: 040/350920-0

fax: 040/350902-61

A description of the BM7 monoclonal antibody can be found at www.medac.de under "product portfolio" -> "diagnostics" -> "products" -> "oncology". A description sheet for the BM7 antibody is enclosed.

The MOC-31 antibody can be obtained from:

Zymed Laboratories, Inc.

458 Carlton Court

South San Francisco, CA 94080

tel.: 800.874.4494

fax: 650.871.4499

The MOC-31 catalog number is 18-0270; mouse anti-EGP-2 IgG₁. A specification sheet for the MOC-31 antibody is enclosed.

Applicant respectfully requests reconsideration of this information and request withdrawal of this rejection.

Claim Rejections - 35 U.S.C. § 103

Claims 1 and 14 remain rejected under 35 USC 103 for the reasons previously set forth in Paper No. 13, Section 10, pages 12-15. The Office Action (Paper No. 16) indicates that the Applicant argues the references individually without clearly addressing the combined teachings. Applicants respectfully traverse the rejection.

The Applicant respectfully disagrees with the opinion of the Office Action and argues that none of the references alone or in combination teach or suggest the present invention, and one of skill in the art would not have looked to the cited references in attempting to derive the claimed invention.

The '254 patent teaches a DNA sequence encoding a GA 733.1 antigen recognized by a GA733 antibody. However, the GA 733.1 DNA sequence, following expression, can be post-translationally modified by glycosylation such that many epitopes are created and therefore the GA 733.1 antigen becomes nonspecific compared to the specific epitope recognized by the MOC 31 MAb. Therefore, the '254 patent is deficient and fails to teach to the current invention.

Second, it is not possible to use the combined teaching of the cited publications. The following essential features and requirements of the claimed invention are not met. First, the present method requires that the correct antibody is bound to the correct antigen and antigen epitope. This is essential both to obtain the required specificity and the activity of the immunotoxin. The combined publications fail to teach this.

Second, the antibodies must be connected to the optimal toxin that is antigen/antibody dependent. This is absolutely necessary in order to obtain the optimal cellular internalization and subsequent high activity. The combined publications also fail to teach this. For example, Lemoli's toxin would not be effectively connected to the present antibody. The teaching of Bjorn together with Lemoli does not suggest the claimed invention due to the rigid requirements regarding the specificity of the claimed method.

Thirdly, all of the cited publications concern *ex vivo* methods and the combination of these fail to teach which antibodies and toxins can be connected to obtain the desired effect, or how these antibody/toxin combinations will work *in vivo*. In the claimed invention the immunotoxin is not affecting healthy tissue but is concentrated in tumor tissue. This is not suggested in the cited publications in combination.

It is known that the antibody is specific in that it will bind to antigens on cancer cells, but the combination of the cited publications did not suggest if the binding of the toxin to the antibody destroyed the antigen-antibody binding capacity. This had to be tested by experimentation.

Applicant respectfully requests consideration these arguments and requests withdrawal of this objection.

New Grounds of Objection - Specification

The Office Action (Paper No. 16) indicates that the amendment filed August 14, 2000 is objected to under 35 U.S.C. 132 because it introduces new matter. Specifically, the Office Action states, "The amended Table 4 replaces the original 1.0 ug/ml with 0.1 ug/ml, retaining the 2.5 log cell kill. There is no supporting the specification as originally filed for a 0.1 ug/ml with a 2.5 log cell kill."

As addressed by the Applicant previously, regarding the Amendment in the specification of Table 4, the 0.1 ug/ml was a result of a clerical error and the amended Table 4 corrects this problem. Applicant has withdrawn Amended Table 4 as submitted in the papers filed 14 August, 2000. Applicant respectfully requests reconsideration of this amendment and requests withdrawal of this objection.

New Grounds of Rejection - Claim Rejections - 35 U.S.C. § 112

The Office Action (Paper No. 16) indicates that Claims 1, 3, 6-8 and 14 are rejected under 35 U.S.C. 112 for lack of written description. Specifically, the Office Action states, "The limitation of active toxin fragments has no clear supporting the specification and the claims as originally filed." Furthermore, the Office action states, "...because claim 1 recites the phrase, "active toxin fragments". It is confusing because it is not clear what type of activity is being claimed."

The Applicant has removed "active" from Claim 1, as detailed in the Amendment. Applicant respectfully requests reconsideration of this amendment and requests withdrawal of this rejection.

CONCLUSION

Applicants respectfully assert that the claims 1, 3, 6-8, 13, and 14 -25, upon entry of this amendment, are in a condition for allowance, and earnestly solicit a notice to that effect.


Applicants believe all of the outstanding objection and rejections have been addressed. If the Examiner has any questions regarding the foregoing, it is respectfully requested that she call the undersigned.

Respectfully Submitted,

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Date

1/30/2001


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Enclosures: Antibody specification sheets; Claims pending upon amendment entry.

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WARRANTY
ZYMED LABORATORIES, INC. WARRANTS THAT THE MATERIALS SOLD MEET ZYMED'S PERFORMANCE SPECIFICATIONS FROM THE TIME OF SHIPMENT UNTIL THE EXPIRATION DATE, IF STORED UNDER THE RECOMMENDED CONDITIONS. NO OTHER WARRANTIES OR GUARANTEES, EXPRESSED OR IMPLIED, ARE PROVIDED, INCLUDING WARRANTIES FOR MERCHANTABILITY OR FITNESS FOR A PARTICULAR PURPOSE. UNDER NO CIRCUMSTANCES SHALL ZYMED BE LIABLE FOR ANY DAMAGES ARISING OUT OF THE USE OF THE MATERIALS.

RELATED PRODUCTS

Specificity	Clone or PAD	Format	Size	Zymed Cat. No.
Mouse anti-SCLC Ig (CD56)	MOC-32	Predilute	6 mL	08-1271
Mouse anti-CD56 (N-CAM)	123C3	Concentrate	1 mL	18-0152
Mouse anti-E-Cadherin	4A2C7	Concentrate	1 mL	18-0223
Mouse anti-E-Cadherin	HECD-1	Concentrate	100	13-1700
Mouse anti-Cytokeratin 5/6	D9/18B4	Concentrate	1 mL	18-0267
Mouse anti-Cytokeratin 7	OV-TL12/30	Concentrate	1 mL	18-0234
Rabbit anti-Calretinin	DC8	Concentrate	1 mL	18-0211

TRADEMARKS

Cheamoun™, Digest-All™, Histogrip™, Histomount™, and Histostain®, HistoTS5050™, NBA™, PicTure™, and Zymed® are trademarks of Zymed Laboratories, Inc.

Mouse anti-Epithelial Glycoprotein 2 (EGP-2) Concentrate Antibody

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ZYMED LABORATORIES INC.
Advancing Science & Medicine Through Immunochimistry

Lot No. 77777777

INTENDED USE

For research use only.

Zymed's monoclonal Mouse anti-EGP-2 concentrate antibody (clone: MOC-31) is intended to qualitatively detect EGP-2 in Formalin-Fixed Paraffin-Embedded (FFPE) tissue sections by immunohistochemical (IHC) staining.

This antibody can be detected using any of the following Zymed IHC kits: PicTure™, NBA™, Histostain®-P, Cap-Plex™, or HistoTS5050™ kits. Kits must be designed to detect mouse primary antibodies (Broad Spectrum or Mouse reactivity).

EPITHELIAL GLYCOPROTEIN 2 (EGP-2)

Epithelial Glycoprotein 2 (EGP-2, also known as ESA, GA733-2, KSA, and Ep-CAM) is an epithelium-associated 40 kDa membrane glycoprotein. It is classified as a SCLC-cluster-2 lung cancer antigen by the TILed International Workshop on Lung Tumor and Differentiation Antigens.^{1a} In normal tissues, monoclonal MOC-31 detects a membrane epithelial antigen and is immunoreactive with pancreas, prostate, brain, kidney, thyroid gland and colon. In tumors, MOC-31 antibody reacts with both SCLC (small cell lung cancer) and non-SCLC. MOC-31 is usually non-reactive in normal and malignant mesothelia and therefore is especially useful for the distinction between lung carcinomas (23 of 23 were strongly positive) and mesotheliomas (1 of 23 was positive-weakly).^{1b} MOC-31 antibody stains adenocarcinoma cells but not reactive mesothelial cells in reactive pleural effusions.^{1b} It has also been reported that MOC-31 antibody is useful for differentiating primary hepatocellular carcinomas (15 of 15 cases were negative) from metastatic adenocarcinomas in the liver (33 of 33 cases were positive).^{2a}

PRINCIPLE OF IHC PROCEDURE

This primary antibody can be used with an immunohistochemical (IHC) detection system. IHC staining techniques allow for the visualization of antigens via the sequential application of a specific antibody to the target antigen (primary antibody) and a secondary antibody reagent that binds to the primary antibody. At some point an enzyme-based reagent is added so that the immunocomplex, which is connected to the antigen, will contain an enzyme. Enzymatic activation of a chromogen results in a visible reaction product at the antigen site. The specimen may then be counterstained and coverslipped. Results are interpreted using a light microscope.

QUANTITY: 1 mL**REAGENT PROVIDED**

Provided as a 1 mL aliquot of Mouse anti-EGP-2 concentrate antibody. This antibody is derived from tissue culture supernatant with 8% Fetal Bovine Serum (FBS), and contains 0.1% Sodium Azide (NaN₃).

IMMUNOGEN: Cells derived from small cell lung carcinoma

CLONE: MOC-31^{1b}

ISOTYPE: IgG₁

Total protein concentration: 777 g/L (BCA protein assay using BSA as a standard)

Mouse Ig concentration: 777 mg/L (E₁ at 280 nm = 14)

USAGE

Zymed's Mouse anti-EGP-2 (clone no. MOC-31) antibody is useful for IHC of FFPE tissue sections.



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SPECIFICITY
This monoclonal antibody (clone: MOC-31) is specific for EGP-2a1

MATERIALS REQUIRED BUT NOT PROVIDED

- | Reagent | Zymed Cat. No. |
|--|----------------|
| 1. Hiscobit™ | 00-8050 |
| 2. PAP Pen | 00-8938 |
| 3. Purified mouse IgG, kappa immunoglobulin (non-immune) | 00-6599 |
| 4. Antibody Diluent | 00-3118 |
| 5. PBS (0.01 M PBS) | 00-3000 |
| 6. Digest-Aid™ 3 | 00-3009 |
| 7. Mayer's hematoxylin | 00-8011 |
| 8. Pictur™, NBA™ kit, or LAB-SA™ kit (Histostain®-Plus, HistoST5050™, and Cap-Plus™) for detecting murine primary antibodies on human samples (other kits are available, call for info.) | |

Table 1. Zymed Immunohistochemistry Detection Kits.

Detection Kits	Enzyme	Chromogen	Size	1° Ab Reactivity	Zymed Cat. No.
Pictur™ (Polymer Kit)	HRP	AEC	15 mL	Broad Spectrum*	87-9943
Pictur™ (Polymer Kit)	HRP	DAB	15 mL	Broad Spectrum*	87-9643
Pictur™ (Polymer Kit)	HRP	DAB	15 mL	Mouse	87-9143
Pictur™ (Polymer Kit)	HRP	—	110 mL	Broad Spectrum*	87-8943
NBA™	HRP	AEC	15 mL	Broad Spectrum*	85-3043
NBA™	HRP	DAB	15 mL	Broad Spectrum*	85-4043
NBA™	HRP	—	60 mL	Broad Spectrum*	85-3243
HistoStain®-Plus	HRP	AEC	15 mL	Broad Spectrum*	85-9843
HistoStain®-Plus	HRP	AEC	15 mL	Mouse	85-6543
HistoStain®-Plus	HRP	DAB	15 mL	Broad Spectrum*	85-9643
HistoStain®-Plus	HRP	DAB	15 mL	Mouse	85-9143
HistoStain®-Plus	HRP	—	60 mL	Broad Spectrum*	85-8943
HistoStain®-Plus	AP	Fast-Red	15 mL	Broad Spectrum*	85-9942
HistoStain®-Plus	AP	—	60 mL	Broad Spectrum*	85-8942
HistoST5050™	HRP	AEC	15 mL	Broad Spectrum*	85-0143
HistoST5050™	HRP	DAB	15 mL	Broad Spectrum*	85-0243
HistoST5050™	AP	Fast-Red	15 mL	Broad Spectrum*	85-0142
HistoST5050™	HRP	AEC	60 mL	Broad Spectrum*	85-1143
HistoST5050™	HRP	DAB	60 mL	Broad Spectrum*	85-1243
Cap-Plus™ Detection Kit	HRP	DAB	110 mL	Broad Spectrum*	87-8143
Cap-Plus™ Buffer Kit				Use with Cap-Plus™ Detection Kit	87-0003

* detects mouse, rabbit, rat, and guinea pig primary antibodies

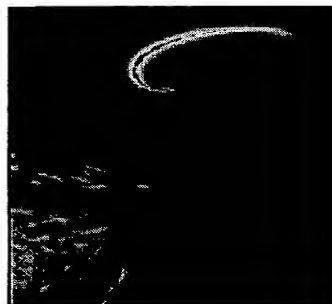
- Chromogen substrate (if not included with detection kit): Single Solution AEC (aminoethyl carbazole, Zymed Cat. No. 00-1111), or DAB (3,3'-diaminobenzidine, 00-2014), or Fast-Red (00-2234).
- Mounting solution: HistoMount™ for DAB (Zymed Cat. No. 00-8030), GVA for AEC or Fast-Red (00-8000), or Clearmount™ for AEC, DAB, or Fast-Red (00-8010).

Also: Coverslips, humidifying chamber, microscope, microscope slides, liner, staining jars, deparaffinizing and rehydrating reagents.

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REFERENCES

- Shen J, et al. Molecular cloning and characterization of a human monoclonal antibody to EGP-2a1 antigen complementing DNA. *Cancer Res* 49(23):1427 (1989).
- Shen J, et al. Antigen of lung cancer: Re-2a1, the first monoclonal antibody on lung tumor and differentiation antigens. *J Natl Cancer Inst* 82(18):669-672 (1990).
- Shen J, et al. Anti-MOC-31: a monoclonal antibody in the pulmonary adenocarcinoma versus metastatic immunohistochemistry panel. *Mod Pathol* 10(7):716-719 (1997).
- Morgan R, et al. MOC-31: a monoclonal antibody in the pulmonary adenocarcinoma versus metastatic immunohistochemistry panel. *Mod Pathol* 10(7):716-719 (1997).
- Shen J, et al. MOC-31: a monoclonal antibody in the pulmonary adenocarcinoma versus metastatic immunohistochemistry panel. *Mod Pathol* 10(7):716-719 (1997).
- Shen J, et al. MOC-31: a monoclonal antibody in the pulmonary adenocarcinoma versus metastatic immunohistochemistry panel. *Mod Pathol* 10(7):716-719 (1997).
- Shen J, et al. MOC-31: a monoclonal antibody in the pulmonary adenocarcinoma versus metastatic immunohistochemistry panel. *Mod Pathol* 10(7):716-719 (1997).
- Shen J, et al. MOC-31: a monoclonal antibody in the pulmonary adenocarcinoma versus metastatic immunohistochemistry panel. *Mod Pathol* 10(7):716-719 (1997).
- Shen J, et al. MOC-31: a monoclonal antibody in the pulmonary adenocarcinoma versus metastatic immunohistochemistry panel. *Mod Pathol* 10(7):716-719 (1997).
- Shen J, et al. MOC-31: a monoclonal antibody in the pulmonary adenocarcinoma versus metastatic immunohistochemistry panel. *Mod Pathol* 10(7):716-719 (1997).
- Shen J, et al. MOC-31: a monoclonal antibody in the pulmonary adenocarcinoma versus metastatic immunohistochemistry panel. *Mod Pathol* 10(7):716-719 (1997).
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- Shen J, et al. MOC-31: a monoclonal antibody in the pulmonary adenocarcinoma versus metastatic immunohistochemistry panel. *Mod Pathol* 10(7):716-719 (1997).
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Oncology:

Cancer Associated Serum Antigen (CASA) belongs to the group of polymorphic epithelial mucins. During the course of malignant transformations, these antigen structures undergo enhanced expression on the surface of epithelial tumour cells. CASA is preferentially expressed on ovarian tumour cells and secreted into the serum. The expression of CASA is independent of other tumour markers (CA 125 and CA 72-4) or is complementary to them.

By using CASA and CA 125 in combination, it has now for the first time become feasible to make a relatively confident assessment of the malignancy or non-malignancy of lower abdominal conditions by using tumour marker values.

TAG 12 is a new serological parameter for monitoring the progress of patients with breast cancer.

The two monoclonal antibodies BM2 and BM7 are employed to detect epitopes of the antigen TAG 12 (Tumor Associated Glycoprotein), which belongs to the group of polymorphic epithelial mucins. BM2 detects a peptide epitope and BM7 a carbohydrate epitope of the mucin. Elevated serum TAG 12 concentrations in breast cancer patients are correlated with active tumour proliferation.

The antibodies employed in the TAG 12 assay recognise mucin 1-epitopes other than those detected by the antibodies used in the CA 15-3 assay.

This new tumour marker is characterised by very high specificity as assessed by testing in healthy subjects and in patients with benign breast lesions. As regards its sensitivity towards malignant breast lesions, there is good correlation between ATG 12 and CA 15-3. The kinetics of the neoplastic process, however, can often be more clearly displayed by TAG 12 determinations.

Thanks to their power to detect several different antigens, parallel determination of TAG 12, CA 15-3 and CYFRA 8/18 provides diagnostic information of greater reliability for monitoring the progress of patients with breast cancer.

Monoclonal mouse antibodies are employed in vivo for immunosuppression after organ transplants, for suppressing acute flare ups in patients with

Pending Claims Upon Entry of the Amendment Filed 03 January, 2001

1. (Thrice amended) Method to kill breast cancer cells or other carcinoma cells expressing target antigens in a cell population selected from the group consisting of cells comprising nucleated cells in peripheral blood and bone marrow cells comprising CD-34⁺ cells selected from the above nucleated cells, wherein the cell population is exposed to a combination of two immunotoxins, wherein each immunotoxin is composed of a conjugate between an antibody and a cell toxin, antigen binding antibody fragments and toxin fragments, or recombinantly produced antibodies, toxins, immunotoxins or fragments thereof, wherein the antibodies are directed to epitopes on the antigen EGP2 expressed by the gene GA733-2 and to epitopes on the antigen expressed by the MUC1 gene and the toxin is Pseudomonas exotoxin A.
3. (Amended) Method according to claim 1, characterized in that the used antibodies are MOC31 and 595A6, or antigen binding fragments thereof.
6. (Amended) Method according to claim 1 wherein said exposure consists of administering the specific immunotoxins *in vivo*.
7. Method according to claim 6, characterized in that the immunotoxins are administered systemically, especially in case of malignant spread to tissues such as bone and bone marrow.
8. Method according to claim 6, characterized in that the immunotoxins are administered directly into the tumor or in the pleural and abdominal cavities.
14. (Amended) The method of claim 1, wherein said exposure consists of administering the immunotoxins *ex vivo*.

15.(New) A method for killing malignant cells in a cell population, the method comprising

obtaining the population of cells *ex vivo* that contains the malignant cells;

contacting the population of cells with at least two immunotoxins, wherein a first immunotoxin comprises a PE molecule conjugated to an antibody or an antibody fragment capable of binding an EGP2 antigen which is expressed by a GA733-2 gene and a second immunotoxin comprising a PE molecule conjugated to an antibody or an antibody fragment capable of binding an antigen encoded by the MUC1, MUC2, or MUC3 gene.

16. (New) The method according to claim 15, wherein the first immunotoxin comprises a PE molecule conjugated to a MOC31 antibody or an antigen-binding antibody fragment thereof, and the second immunotoxin comprises a PE molecule conjugated to a 595A6 antibody or an antigen-binding antibody fragment thereof.

17. (New) The method according to claim 15, wherein the cell population is obtained *ex vivo* from a cancer patient.

18. (New) The method according to claim 17, wherein the cell population comprises peripheral blood cells or bone marrow cells.

19. (New) The method according to claim 18, wherein the cell population comprises CD34+ cells

20. (New) The method according to claim 19, wherein the cell population is enriched or positively selected for CD34+ cells.

21. (New) The method according to claim 1 wherein treatment of the cell population with the two or more immunotoxins causes low toxicity to CD34+ cells in the population.

22. (New) A method for killing malignant cells in a patient, the method comprising administering to the patient a therapeutically effective amount of at least two immunotoxins, wherein a first immunotoxin comprises a PE molecule conjugated to an antibody or an antibody fragment capable of binding an EGP2 antigen which is expressed by a GA733-2 gene and a second immunotoxin comprises a PE molecule conjugated to an antibody or an antibody fragment capable of binding an antigen encoded by the MUC1, MUC2, or MUC3 genes.

23. (New) The method according to claim 22, wherein the patient is a cancer patient.

24. (New) The method according to claim 22, wherein the malignant cells are carcinomas.

25. (New) The method according to claim 1 wherein treatment of the cell population with the two or more immunotoxins causes low toxicity to CD34+ cells in the population.

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